

Original Article

Influence of BsmI polymorphism in vitamin D receptor gene on the risk of fracture in Caucasian populations: a meta analysis

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Abstract: Objective: To gain combined risk estimates for the BsmI polymorphism in vitamin D receptor (*VDR*) gene associated with the risk of fractures in Caucasian population. Methods: We performed a meta-analysis and extracted 15 eligible publications by searching the databases of Medline, EMBASE and CNKI. Summary odds ratio (OR) with 95% confidence interval (CI) was estimated by using fixed-effects model. The inconsistency index (I^2) was performed to evaluate heterogeneity. Begg's funnel plots and Egger's test were used to assess publication bias. Results: A total of 15 available studies including 5,570 subjects (1,912 cases and 3,658 controls) were included in the meta-analysis. No overall association was observed between the BsmI polymorphism in *VDR* gene and the susceptibility to fracture under all genetic models. When stratifying by fracture type, we did not find any significant risk, either. But in the subgroup analysis by source of control, the results from population-based groups suggested the BsmI polymorphism was associated with the increased fracture susceptibility ($OR_{BB\ vs.\ bb} = 1.22$, 95% CI = 1.01-1.48, $P_{heterogeneity} = 0.912$; $OR_{B\ vs.\ b} = 1.10$, 95% CI = 1.00-1.20, $P_{heterogeneity} = 0.921$). Conclusions: Our meta-analysis provides evidence that the BsmI polymorphism in *VDR* gene may not be associated with the susceptibility to fracture in Caucasian populations. Our findings need to be further confirmed in future larger and well-designed studies.

Keywords: *VDR*, polymorphism, fracture, risk

Introduction

Osteoporosis characterized by microarchitectural deterioration of bone tissue and reduced bone mass is a systemic disease and would cause increased bone fragility and fracture. The causes leading to osteoporosis mainly include severe environmental and genetic factors [1]. The role of genetic factors, such as the genetic polymorphisms of BsmI, TaqI, Apal and FokI in the vitamin D receptor (*VDR*) gene in fracture risk has been extensively reported [2-8]. But the exact association has failed to be well-defined and still remains to be further evaluated.

Vitamin D regulates bone metabolism via its role in mediating calcium homeostasis as well as the effect on osteoblasts [9]. The activity of vitamin D is mediated by *VDR*. Great efforts have been made to estimate the relationships between the above-mentioned polymorphisms

and the risk of fracture. Nevertheless, the most frequently investigated one is the BsmI polymorphism [1, 10-15].

There have been two studies investigating whether the polymorphisms in *VDR* were associated with fracture risk by meta-analysis [2, 3]. However, the findings were inconsistent rather than conclusive. Moreover, the investigation focusing on the BsmI polymorphism in *VDR* and the risk of fracture has not been reported to date. So we conducted a comprehensive and systematic meta-analysis in order to more precisely estimate the correlation of this polymorphism in *VDR* with fracture risk.

Materials and methods

Literature search strategy

To include all case-control association studies of fracture with sufficient genotyping data of

Bsm1 polymorphism in vitamin D receptor gene and risk of fracture

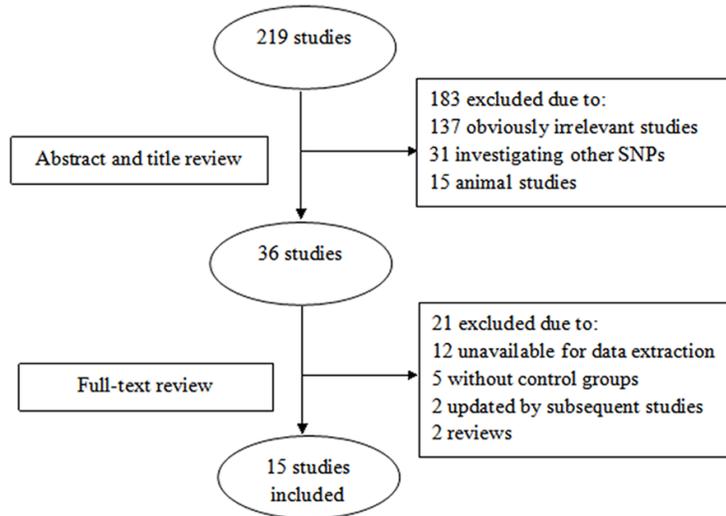


Figure 1. The flow chart of the included studies.

the Bsm1 polymorphism, we conducted a comprehensive search of the databases including Medline, EMBASE and CNKI for eligible literature. The following terms were used in this search: “Vitamin D receptor” or “VDR”, “Bsm1”, “Bsm1 polymorphism” or “genetic polymorphism”, combined with “fracture”. There was no language limitation except that the extracted studies must be conducted on human subjects. The references of the relevant articles and review articles were manually-screened to recruit more available original articles.

Inclusion and exclusion criteria

The designed inclusion criteria were as follows: (1) a case-control study; (2) an investigation between Bsm1 polymorphism and fracture risk; (3) providing total numbers of cases and controls; (4) detailed genotyping data in both case and control groups. The following were the exclusion criteria: (1) without adequate data to calculate an odds ratio (OR) with 95% confidence interval (CI); (2) overlapping data, if more than one published study used the same case series, the one with the largest sample size or more detailed genotyping information was selected; (3) abstract, comment, review and editorial.

Data extraction

Two reviewers extracted the data independently according to the mentioned inclusion and exclusion criteria above. Disagreements were solved by discussion or turning to a third review-

er. The following items must be extracted from all eligible publications: first author, publication year, ethnicity, country of study, genotyping method, fracture type, source of controls, numbers of cases and controls, numbers of Bsm1 genotypes in cases and controls, and study results. Besides, the studies were classified as hospital-based study or population-based study according to sources of controls. Finally, 15 case-control studies were available for this meta-analysis.

Statistical analysis

The strength of the correlation between the Bsm1 polymorphism in *VDR* gene and fracture risk was estimated via calculating the crude odds ratio (OR) with 95% confidence interval (CI). We assessed five genetic models: BB vs. bb, BB + Bb vs. bb, BB vs. Bb + bb, B vs. b, and Bb vs. bb. The I^2 statistic was adopted to quantify the proportion of the total variation due to heterogeneity. An $I^2 < 0.05$ indicates a lack of heterogeneity among studies [16, 17]. Then, the fixed-effects model (the Mantel-Haenszel method) was adopted to pool the data [18]. Instead, if $I^2 > 0.05$, the random-effects model (the DerSimonian and Laird method) was used [19]. Sensitivity analysis was performed to assess the credibility of outcomes in this meta-analysis by sequential omission of individual studies. The publication bias was validated by visual inspection of the funnel plot [20]. Hardy-Weinberg equilibrium (HWE) among controls for each study was examined by the Pearson’s goodness-of-fit chi-square test. All statistical analyses were performed with Stata version 12.0 (Stata Corp LP, College Station, Texas). $P < 0.05$ was considered statistically significant.

Results

Study characteristics

We extracted a total of 219 articles from the searched databases, and only 15 satisfied our inclusion criteria (**Figure 1, Table 1**). Of the included studies, one was carried out by using the same controls [1]; four studies investigated two separate subject groups in the same article

BsmI polymorphism in vitamin D receptor gene and risk of fracture

Table 1. Main characteristics of all studies included in the meta-analysis

| Authors | Country of study | Gender (F/M) | Fracture type | Source of control | Genotyping method | HWE |
|--------------------------|------------------|--------------|---------------|-------------------|-------------------|-------|
| Aerssens et al. | Belgium | F | Hip | Hospital-based | PCR | 0.459 |
| Alvarez-Hernandez et al. | Spain | M | Vertebral | Population-based | PCR | 0.618 |
| Berg et al. | Norway | F | Nonvertebral | Population-based | PCR | 0.156 |
| Chatzipapas et al. | Greece | M/F | Stress | Hospital-based | PCR-RFLP | 0.219 |
| Feskanich [1] et al. | USA | F | Hip | Population-based | PCR | 0.770 |
| Feskanich [2] et al. | USA | F | Forearm | Population-based | PCR | 0.152 |
| Gomez [1] et al. | Spain | F | Vertebral | Population-based | PCR | 0.241 |
| Gomez [2] et al. | Spain | M | Vertebral | Population-based | PCR | 0.594 |
| Garnero 1 et al. | France | F | Vertebral | Population-based | PCR | 0.708 |
| Garnero [2] et al. | France | F | Nonvertebral | Population-based | PCR | 0.708 |
| Houstan et al. | UK | F | Vertebral | Population-based | PCR | 0.450 |
| Host-Sikorska et al. | Poland | F | Any | Hospital-based | PCR-RFLP | 0.215 |
| Host-Sikorska et al. | Poland | M/F | Any | Hospital-based | PCR-RFLP | 0.339 |
| Langdahl [1] et al. | Denmark | F | Vertebral | Hospital-based | PCR-RFLP | 0.186 |
| Langdahl [2] et al. | Danmark | M | Vertebral | Hospital-based | PCR-RFLP | 0.089 |
| Quevedo et al. | Chile | F | Hip | Hospital-based | PCR | 0.046 |
| Ramalho et al. | Brazil | F | Hip | Hospital-based | PCR-RFLP | 0.050 |
| Valimaki et al. | Finland | F | Hip | Population-based | PCR | 0.253 |
| Wengreen et al. | USA | F | Hip | Population-based | PCR-RFLP | 0.043 |

PCR: polymerase chain reaction; PCR-RFLP: PCR-restriction fragment length polymorphism; HWE: Hardy-Weinberg equilibrium.

[1, 8, 10, 14]. The characteristics of the included studies in our meta-analysis were summarized in **Table 1**. The fracture type was categorized into hip, vertebral, non-vertebral, forearm and any types. All studies were case-control designs based on Caucasian populations and were age- and gender-matched healthy controls. This meta-analysis combined a total of 5,570 subjects including 1,912 cases and 3,658 controls. The genotype distribution of all controls was in accordance with HWE except slight deviation in two [15, 23].

Quantitative synthesis

When all eligible studies were pooled into one dataset for the meta-analysis, we found no statistical association between the between the BsmI polymorphism in VDR gene and fracture risk in all comparison models ($OR_{BB\ vs.\ bb} = 1.13$, 95% CI = 0.96-1.32, $P_{heterogeneity} = 0.577$; $OR_{BB\ +\ Bb\ vs.\ bb} = 1.05$, 95% CI = 0.95-1.15, $P_{heterogeneity} = 0.988$; $OR_{BB\ vs.\ Bb\ +\ bb} = 1.08$, 95% CI = 0.93-1.26, $P_{heterogeneity} = 0.836$; $OR_{B\ vs.\ b} = 1.06$, 95% CI = 0.98-1.14, $P_{heterogeneity} = 0.757$; $OR_{Bb\ vs.\ bb} = 1.05$, 95% CI = 0.95-1.18, $P_{heterogeneity} = 0.990$). Similarly, little association was observed between fracture type and fracture risk in the

stratified analysis. In the subgroup analysis by source of control, however, the risk for the allele B, compared with the allele b, was 1.10 ($OR_{B\ vs.\ b} = 1.10$, 95% CI = 1.00-1.20, $P_{heterogeneity} = 0.921$). The individuals with BB genotype had 1.22-fold higher risk, as compared with those carrying bb genotype ($OR_{BB\ vs.\ bb} = 1.22$, 95% CI = 1.01-1.48, $P_{heterogeneity} = 0.912$). But no significant association was found in any of the genetic models among hospital-based populations (**Table 2, Figures 2 and 3**).

Heterogeneity and sensitivity analyses

There was no between-study heterogeneity across the included studies in our meta-analysis. In the sensitivity analyses, we checked the influence of each study on the pooled OR by omitting each study, one at a time and recalculating the OR with 95% CI. We found no alteration in our results when excluding each study, suggesting the stability of our findings.

Bias diagnostics

Begg's funnel plot and Egger's test were adopted to diagnose the publication bias of the included studies. The symmetrical shape of the

BsmI polymorphism in vitamin D receptor gene and risk of fracture

Table 2. Results of pooled ORs in the meta-analysis

| | BB vs. bb | | BB + Bb vs. bb | | BB vs. Bb + bb | | Allele B vs. Allele b | | Bb vs. bb | |
|-------------------|-------------------|-------|-------------------|-------|-------------------|-------|-----------------------|-------|-------------------|-------|
| | OR (95% CI) | P_h | OR (95% CI) | P_h | OR (95% CI) | P_h | OR (95% CI) | P_h | OR (95% CI) | P_h |
| Fracture type | | | | | | | | | | |
| Hip | 1.21 (0.98, 1.50) | 0.467 | 1.07 (0.95, 1.21) | 0.822 | 1.16 (0.95, 1.41) | 0.648 | 1.09 (0.99, 1.21) | 0.580 | 1.08 (0.93, 1.24) | 0.757 |
| Vertebral | 1.07 (0.73, 1.55) | 0.951 | 1.05 (0.84, 1.31) | 0.962 | 1.00 (0.71, 1.42) | 0.998 | 1.04 (0.86, 1.24) | 0.915 | 1.07 (0.82, 1.39) | 0.938 |
| Any | 0.98 (0.70, 1.37) | 0.101 | 0.99 (0.82, 1.20) | 0.682 | 0.99 (0.72, 1.35) | 0.175 | 0.99 (0.85, 1.16) | 0.152 | 1.00 (0.81, 1.24) | 0.806 |
| Source of control | | | | | | | | | | |
| Hospital | 0.93 (0.69, 1.26) | 0.207 | 0.97 (0.82, 1.16) | 0.773 | 0.90 (0.82, 1.16) | 0.600 | 0.96 (0.83, 1.11) | 0.336 | 0.99 (0.80, 1.21) | 0.776 |
| Population | 1.22 (1.01, 1.48) | 0.912 | 1.08 (0.97, 1.20) | 0.994 | 1.17 (0.98, 1.40) | 0.918 | 1.10 (1.00, 1.20) | 0.921 | 1.08 (0.95, 1.23) | 0.992 |
| Total | 1.13 (0.96, 1.32) | 0.577 | 1.05 (0.95, 1.15) | 0.988 | 1.08 (0.93, 1.26) | 0.836 | 1.06 (0.98, 1.14) | 0.669 | 1.05 (0.95, 1.18) | 0.990 |

P_h : P -value of heterogeneity test. CI: confidence interval; OR, odds ratio.

Bsm1 polymorphism in vitamin D receptor gene and risk of fracture

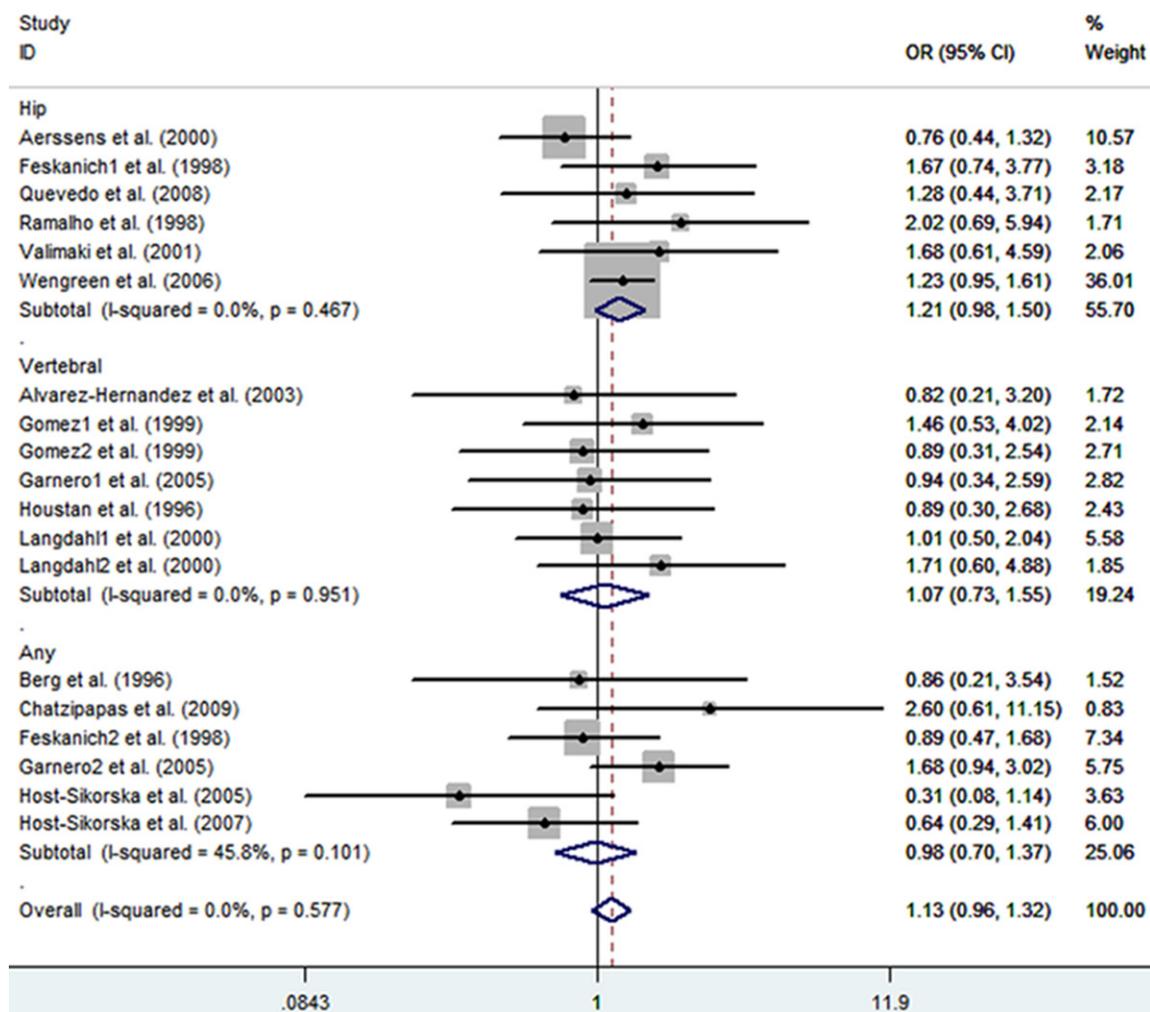


Figure 2. Forest plot of fracture risk associated with the Bsm1 polymorphism stratified by ethnicity under BB vs. bb model. The boxes and horizontal lines represent the OR and the corresponding 95% CI. The area of the boxes indicates the weight (inverse of the variance). The diamond corresponds to the summary OR and 95% CI. No significant association between the Bsm1 polymorphism and fracture risk was observed.

funnel plots did not indicate any evidence of obvious bias (Figure 4). Then Egger's test was performed and provided statistical evidence of funnel plot symmetry. These results revealed no obvious publication bias in our meta-analysis (BB vs. Bb: Begg's test: $P = 0.234$; Egger's test: $P = 0.250$).

Discussion

Association studies are considered as a mighty way of evaluating the association between genetic factors and susceptibility to common disorders like osteoporosis [24]. However, the individual association studies with controversial findings fail to estimate the potential modest genetic effects on the susceptibility to common diseases [25], which might result from the

differences in study design, study populations and sample sizes. But meta-analysis is capable of resolving these disadvantages by a systematic collection of the single studies, thus increasing the statistical power to identify an association and enhancing the precision of the correlation [26].

Overall, no significant fracture risk associated with the Bsm1 polymorphism was observed when all studies were pooled into the meta-analysis. One possible explanation is that the Bsm1 polymorphism is a low-penetrant single nucleotide polymorphism with a very weak effect that needs a much larger study to detect. Our results were consistent with two previous published studies which also revealed that no relationship of the VDR Bsm1 polymorphism and

Bsm1 polymorphism in vitamin D receptor gene and risk of fracture

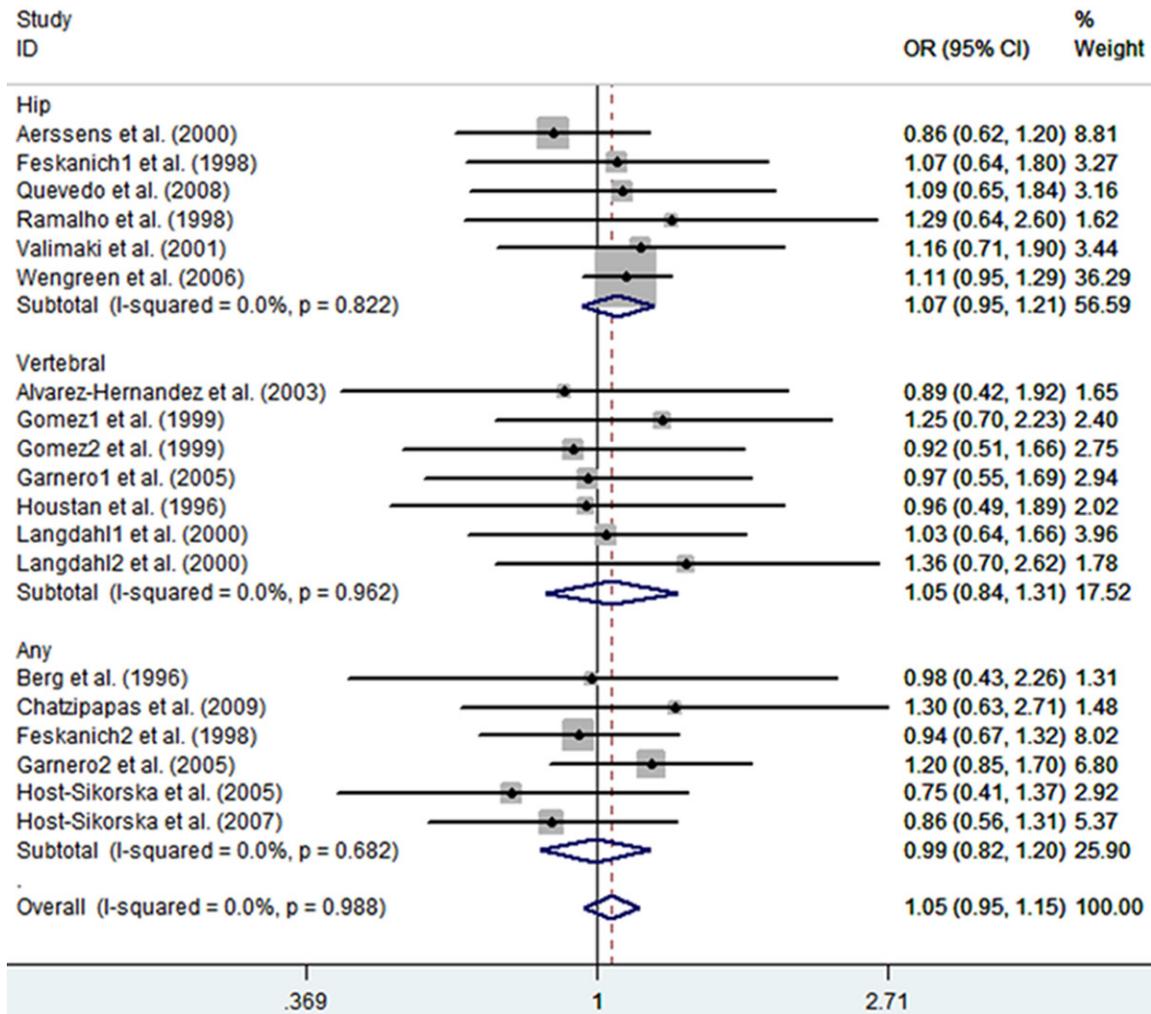


Figure 3. Forest plot of fracture risk associated with the Bsm1 polymorphism stratified by ethnicity under BB + Bb vs. bb model. The boxes and horizontal lines represent the OR and the corresponding 95% CI. The area of the boxes indicates the weight (inverse of the variance). The diamond corresponds to the summary OR and 95% CI. No significant association between the Bsm1 polymorphism and fracture risk was observed.

fracture risk was found in the meta-analysis of published data [3, 27]. However, another study including four polymorphisms of Bsm1, Apal, Taql, FokI demonstrated that there was a modest but statistically significant association between the Bsm1 bb genotypes and fracture [2]. It is suggested that the Bsm1 polymorphism does not independently modify the fracture risk, but the interaction with other polymorphisms may affect the overall assessment of the association.

To further identify our results, subgroup analysis by fracture type and source of control were carried out. In the stratified analysis by fracture type, we observed no fracture risk in relation to

the Bsm1 polymorphism. Nonetheless, in the subgroup analysis by source of control, the results from population-based groups revealed significant association between this polymorphism and fracture susceptibility. Several meta-analyses have reported Bsm1 polymorphism was correlated with bone mineral density (BMD). One implicated the BB genotype of the Bsm1 polymorphism was relevant to low BMD only at the hip and that younger women with BB genotype had borderline significant lower BMD in comparison with those with the bb genotype [28]. In another meta-analysis, the results revealed that Bb + bb genotypes had higher spine BMD than BB genotype only in studies of postmenopausal women with a big range of B allele

Bsml polymorphism in vitamin D receptor gene and risk of fracture

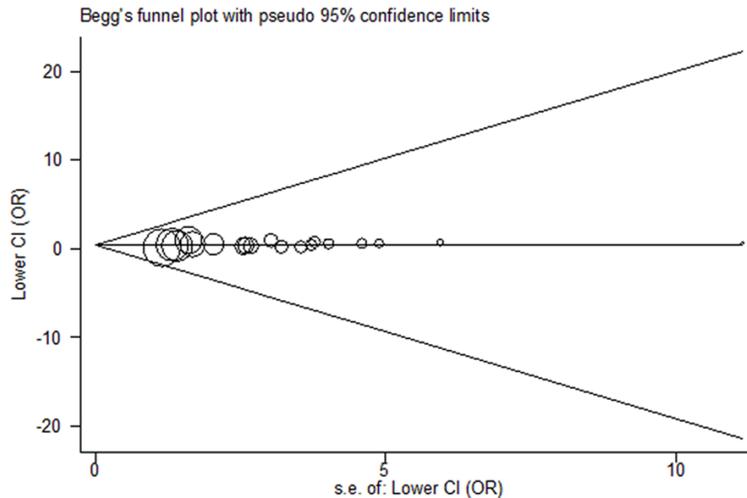


Figure 4. Begg's funnel plot for the Bsml polymorphism. Each circle dot represents a separate study for the indicated association between the Bsml polymorphism and fracture risk under BB vs. bb model (Begg's test: $P = 0.234$; Egger's test: $P = 0.250$).

frequency (29-53%) [25]. These results imply that B allele may have more associations with fracture risk, compared to the b allele. Moreover, the correlation between Bsml polymorphism in *VDR* gene and other diseases has been explored by several meta-analyses [29-31], suggesting its crucial role in these diseases.

However, an increased risk was found in population-based studies, but not in hospital-based studies. This might result from selection bias. Because not all the selected control populations could truly represent the general population, and the recruitment criteria were not uniformly designed in the included studies. Thus representative controls should be used in further studies.

The potential limitations need to be addressed in this current study. First, our meta-analysis was conducted on Caucasians alone, so future studies with more ethnic groups are needed to comprehensively estimate the possible effects of the Bsml polymorphism on fracture risk in different ethnicities. Besides, publication bias may have occurred, although no obvious bias was observed in the bias diagnostics. Because only published studies were included in our meta-analysis.

In summary, our meta-analysis suggested that the Bsml polymorphism in *VDR* gene was not associated with the overall risk of fracture in Caucasian population. But significant association was observed in the stratified analysis by

source of control in population-based groups. These results implicated that the Bsml polymorphism in *VDR* gene might play a role in fracture susceptibility. However, more prospective studies with larger samples and various ethnic groups are still required to further confirm the associations.

Disclosure of conflict of interest

None.

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